Icosapent Ethyl for Cardiovascular Risk Reduction: Who and When

Podcast Transcription

May 28, 2020

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This program was developed by the Canadian Collaborative Research Network (CCRN) and was supported through an unrestricted educational grant received from HLS Therapeutics. Our program today is entitled *Icosapent Ethyl for Cardiovascular Risk Reduction: Who and When*. My name is Milan Gupta, from McMaster University and CCRN, and I'm pleased to be joined today by my good colleague, Dr. Shaun Goodman, from the University of Toronto and St. Michael's Hospital. Shaun, welcome.

SG: Thanks Milan, it's a pleasure to be speaking with you.

MG: This podcast is the first in a series of podcasts programs on this title. The next podcast coming soon will be focused on triglycerides. So watch out for that one.

MG: So, Shaun, today we're going to talk about the role of managing the risk associated with high triglycerides in trying to reduce cardiovascular events. As you know, we have long debated in the medical literature whether triglyceride levels predict risk and whether or not they should be a target of therapy. And so by way of introduction, I thought I would just go over a little bit of the data that we have before turning it over to you. We've done some very large contemporary trials of LDL lowering, notably, the most recent trials being FOURIER[1] and ODYSSEY OUTCOMES[2]. Both of these trials were conducted in really quite

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high risk atherosclerotic cardiovascular disease (ASCVD) patients who had PCSK9 inhibitor, compared to placebo, when added to standard treatment. And while both trials were positive and patients achieved very low LDL levels, we saw that even in patients with such low on-treatment LDL levels, at roughly three to four years their risk of having a recurrent cardiovascular event ranged from 12 to 14%. And we term that residual risk. So even though the LDL is under excellent control, and these patients are receiving all of the other evidence-based therapies, they continue to accrue risk. Now, we know that cardiovascular risk is due to many different factors (diabetes, hypertension, inflammation, thrombosis) but one of the lipid risks factors or markers that has caused us a lot of controversy over the years has been serum triglycerides. I think perhaps the most definitive evidence to date came to us by way of the Emerging Risk Factors Collaboration[2], who, in a meta-analysis of over 300,000 patients, showed a strong linear relationship between non-fasting triglycerides and risk of ischemic heart disease, and a separate, not so strong but significant relationship between triglycerides and ischemic stroke. We also have very contemporary data from the province of Ontario in the CANHEART Study[3], where roughly 200,000 ASCVD patients were evaluated, showing that same linear relationship between triglycerides and cardiovascular risk. So, Shaun, maybe I'll get you to give us some of your thoughts on this. I think triglycerides, we can agree, predict risk. If you have elevated triglycerides, you're at higher risk than if you have normal triglycerides. The question that comes from that is, does lowering triglycerides make a difference? And we have done a number of studies, particularly using fish oils, to try to answer this question. I wonder if you might take us through this.

SG: The fish oil approach, in particular to lower triglycerides, has obviously been undertaken over many years. But the challenge, like anything, is to get the right combination and permutation that confers benefit in clinical outcomes, not just hopefully in things like triglyceride lowering, but is also safe. Typically commercial fish oils that we can buy over-the-counter without really any regulatory oversight, they're really sort of a bouillabaisse, or a mixed bag. They contain a variety of things, including a mixture of the omega-3 and/or the omega-6 fatty acids, that purportedly have benefits from a triglyceride-lowering perspective and maybe some other benefits as well. Some of the earlier studies that we can talk about further that use a grab bag of fish oils probably didn't have the right components. And so omega-3 has really been the focus. We can even drill down further; omega-3 fatty acid's most active ingredients are two compounds that are very similar, but differ. These are DHA and EPA. The latter, EPA, stands for eicospenaetoic acid. There is now a highly purified form of EPA called icosapent ethyl. This is particularly unique and was recently demonstrated, as we'll discuss further, to be of significant benefit in the REDUCE-IT trial[4]. I do want to talk a little bit about the differences even between DHA and EPA because, besides having different numbers of carbon bonds and double bonds at a molecular level, this is probably important as it relates to their independent effects on the membrane structure and the distribution of cholesterol as one example, the ability to inhibit oxidation of lipids, and the ability to inhibit the formation of crystals, that cholesterol crystals that can actually protrude into the coronary artery or in any of the arteries of the arterial tree in the body. In contrast, the DHA components don't contribute in the same way that EPA does to the stability of the membrane. DHA doesn't have the same sort of antioxidant content. And so there's reason to believe that we ultimately need something very purified out of this

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starting point of fish oils and then down to omega-3 fatty acids before we can get something that has a beneficial effect.

Now, you know, Milan, we've obviously lived through a number of triglyceride-lowering outcome studies over the course of time with other therapies like fibrates, which are commercially available, and like niacin. The challenge, of course, is that in all of those trials, particularly when they were added to statin therapy in appropriate patients, there was triglyceride lowering, but there was no improvement in clinical outcomes. No particular benefits that were seen. And so we can come at this from 'let's lower the triglycerides' because this will, in theory, translate to reduction in cardiovascular outcomes because triglycerides are clearly at least a marker for high risk. Thus far, any of the triglyceride-lowering therapies in clinical trials have been reasonably underwhelming or disappointing. There are a number of meta-analyses that have since come along to pool all of the large clinical outcome trials that have looked at things like fibrates and niacin, but also fish oils in particular. And there's a whole laundry list of acronyms that people are probably familiar; the ASCEND trial, Omega ORIGIN[5], vital STRENGTH[6], a more recent study. In a recent meta-analysis of fish oils that included all of these trials, even though one can demonstrate, compared to placebo control, reductions in triglycerides, we really haven't been impressed in any way with the reduction in overall outcomes. There might be a really tiny signal with respect to the lowering of coronary heart disease events, but not statistically significant, even in a meta-analysis. And then there's been some concern that there might be an increased risk. Some of the benefits of some of these therapies including fish oils might be their antiplatelet effects, but in the brain, this could lead potentially to an increased risk of bleeding. And so numerically, there was no difference in stroke outcomes with respect to fish oil trials, but numerically, there were some concerns that overall really didn't make it an attractive therapy, i.e. just general fish oils as a means of lowering triglycerides that would translate into benefits.

MG: Okay, thanks, Shaun. That's very helpful and a little sobering that we have such strong evidence that higher triglycerides seem to be bad for you, but we haven't been able to find a way to reduce that risk. That is until now. You mentioned icosapent ethyl, a very purified prescription form of EPA. That entity was tested in the recent REDUCE-IT trial[4]. And just by way of background, there was an earlier study years ago called the JELIS[7] study that was conducted in Japan with a lower dose of EPA. That trial had some methodological flaws, but at the end of the day, it did show a significant reduction in cardiovascular events with pure EPA. The REDUCE-IT trial builds on that using this now purified form of EPA, called icospent ethyl, or shortened to IPE. In REDUCE-IT, they enrolled high risk patients across the board. Either those who already had established CVD and were at least 45 years of age, or those who were 50 or older with diabetes and additional risk factors, but who did not yet have overt CVD. These patients had to have a triglyceride level fasting of over 1.5 mmol/L, and they had to have a reasonable LDL level, anything under 2.6. They were then randomized to icosapent ethyl 2g BID, so a fairly high dose, or placebo. This was a fairly standard high risk patient population. About 70% of them fell into the secondary prevention cohort. Statin use was excellent with the overwhelming majority on moderate to high intensity statin. And the baseline LDL level was around 1.9 to 2, so well-treated patients with respect to LDL. The baseline triglyceride level was 2.4. Remember, it had to be above 1.5 to get into the study. The study was an astounding success. At about five years, the broad primary composite endpoint was reduced by 25%, with

a very highly significant number needed to treat of 21 at five years. The key secondary endpoint that we're used to when we compare trials, CV death, MI, and stroke, was reduced by 26%, also highly significant, with a number needed to treat of 28. Impressively, we also saw a significant 20% reduction in cardiovascular death in favor of IPE, with a trend but non-significant reduction in total mortality. There were a couple of key findings from subgroups. The patients that had CVD clearly benefited. The patients that had diabetes with risk factors had a similar magnitude of benefit, suggesting consistent benefit across these two different patient types. And also, patients with lower versus higher triglycerides within the context of having to have elevated triglycerides to get in, also had similar benefit. IPE was very well tolerated. The only adverse events that were significantly more frequently noted in icosapent ethyl arm were peripheral edema, constipation, and interestingly, atrial fibrillation. However, there was no increase in stroke, if anything, there was a reduction in stroke. In a very recent, very provocative analysis, the investigators showed us that the overwhelming majority of the benefit seen with icosapent ethyl was not driven by lowering of triglycerides, but in fact was driven by how high the EPA levels were in the serum.

MG: So, here for the first time, we've shown that if we use triglycerides as a marker of risk within a high risk population and then use a specific agent, in this case icosapent ethyl, we can actually reduce major cardiovascular events. So Shaun, I'd like you to comment or reflect on your opinion of the REDUCE-IT trial. And then let's just have a bit of a discussion about how do we operationalize these findings in clinical practice. How do we find the right patient? Who should be on icosapent ethyl for optimal risk reduction?

SG: Thanks, Milan. I think that this is an incredibly impressive trial that can be immediately translated into a benefit for our patients. As a cardiologist, like yourself, the vast majority of the patients that I think this trial and these results are applicable to, are those with clinical atherosclerotic cardiovascular disease and in my practice, that's mainly going to be coronary artery disease like prior myocardial infarction. But even patients with stable coronary artery disease, and patients who have polyvascular disease that don't just have coronary disease but have disease in other arterial beds like peripheral arterial disease of the lower extremities or cerebrovascular disease, will benefit. The trial included that broad group of individuals with a clinical athersclerotic cardiovascualr disease. They did set a lower threshold in terms of age. But to be honest with you, I think, and having participated in other trials myself, you always have to start with a high enough risk patient population to be able to show a benefit or a potential benefit of a therapy. It's not to say that I don't think that IPE would be beneficial to someone who's 44 years of age versus 46 years of age if they otherwise met the eligibility criteria. I'm happy to lower that age clinically. Of course, the question around what is an elevated triglyceride is an open question. The trial again, like any good trial, has to have a definition. And that, as you mentioned before, came in around the lower threshold triglycerides of 1.5. You know, back when I started looking after patients 25-30 years ago, 1.5 wouldn't have been considered elevation of triglycerides, but as you nicely described before, it's a continuous relationship between triglycerides, so-called elevation or at least numeric, values of triglycerides and increase risk of all kinds of cardiovascular events, including all-cause mortality. One could argue that's a somewhat arbitrary window, but I think it's a reasonable starting point, even, as you nicely pointed out, that the IPE benefit here is probably driven a lot by things other than triglyceride lowering. So I think that that's the patient population. It's a fairly broad patient population. Of course, we're going to focus on other modifiable risk factors, as you mentioned at the beginning, like lowering LDL cholesterol, but we

know about the residual risk despite therapy like statins in individuals whose LDL cholesterol is decently controlled or in the target range that the clinician and the patients are happy with on statin. I think if the triglycerides are above 1.5, and they've got some of those other clinical cardiovascular risk features, I think it's really a no brainer to initiate icospent ethyl.

MG: I completely agree with you, Shaun. Just a couple of clarifications for our audience. What about the patient with diabetes and risk factors but who doesn't have a CVD? They were a substantial subgroup of REDUCE-IT, with seemingly consistent benefit. Would you consider them for treatment?

SG: Absolutely. I don't typically see those individuals in my routine clinical practice. And that's why I focused on the clinical atherosclerotic cardiovascular disease cohort. But you're absolutely right. Those individuals who were 50 years of age or older, who had diabetes and at least one risk factor for atherosclerotic cardiovascular disease, even if they didn't yet have manifest athersclerotic cardiovascular disease, benefited to the same degree as those with clinical atherosclerotic cardiovascular disease. And so I think, based on our previous understanding that people who have diabetes, particularly of a reasonable duration and/or mid to older age, and then if you add another risk factor on top of it, their risk of having a cardiovascular event or dying from a cardiovascular event is probably almost identical to who somebody who has had a myocardial infactrion 10 years ago.

MG: You know, this trial reminds me a lot, and I risk giving away our age, Shaun, of the HOPE[8] study with ramipril, which was done in a fairly similar heterogeneous population, secondary prevention, and those with diabetes and risk factors. Ramipril actually reduced cardiovascular risk and our guidelines changed. For everyone with diabetes over the age of 50, or a certain duration of diabetes, the guideline said add an ACE inhibitor for vascular protection. This sort of falls into that same boat wouldn't to say?

SG: I agree. This is a quote unquote vascular protective approach. It's been demonstrated, as you say, with ACE inhibition, like in the HOPE trial. We, of course, are going to manage these patients with clinical atherosclerosis cardiovascular disease, as I mentioned, with LDL lowering, and there will be anti-thrombotic or antiplatelet therapy. But the residual risk beyond that management demands an additional therapy. And in this case, we've got the great REDUCE-IT trial results that can target probably a whole bunch of things, not only triglyceride reduction, but probably there's some anti-thrombotic, antiplatelet effect of the purified EPA of IPE. There are demonstrated measures of inflammation reduction. So there's probably an anti-inflammatory effect that contributes. I think having this unique therapy to target other aspects of the residual cardiovascular risk is a welcome therapy for sure.

MG: Now, let me ask you one other thing, a practical matter for our listeners. Do we need to get a fasting triglyceride level in order to determine whether a patient qualifies for icosapent ethyl or can a non-fasting sample, which is what we generally order for risk assessment, be used?

SG: I think in the vast majority of cases, both for measuring triglycerides and other aspects of the liver profile, a non-fasting approach is the way to go. The guidelines that you are part of in Canada and elsewhere in the world, based on a number of studies, have made the recommendation that we routinely check lipid profiles including triglycerides in a non-fasting way. This makes it easier for the patients and the triglycerides are probably the most sensitive to a fasting versus non-fasting state. But unless the

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triglycerides are extremely elevated, in which case one can always, in a very small minority of cases, repeat when patients are fasting, in the vast majority of cases, the information is going to be valuable. This is another art rather than the science of medicine where I would say, even though a clinical trial like REDUCE-IT would demand a lipid profile, including triglycerides that are in a fasting state, I would be quite content to use a non-fasting result.

MG: I agree completely. And my last point, Shaun, is, you discuss with us the difference between standard over-the-counter fish oils, the different combinations of EPA and DHA in various fish oils, and how icosapent ethyl is different. But again to drive home the point, is there any way we could try to mimic these REDUCE-IT results by using our favorite over-the-counter fish oil?

SG: Unfortunately, it's a definitive no. It would be great if we could, but as as we discussed, it's taken this very highly purified form of fish oil, down to even breaking down the omega fatty acids and purifying them even further to EPA, specifically the IPE product, that's really the only therapy that's been demonstrated to improve outcomes in the REDUCE-IT trial and you mentioned the previous JEALOUS study. So it appears we need a very purified and high dose. If you try to get the equivalent in over-the-counter fish oils, my understanding would be to even get those types of levels you'd be having bucketfuls a couple times a day versus this two simple pills, 2 grams a day, of IPE. Plus there's a whole bunch of kind of toxins, mercury, and other things that unfortunately get into that get into fish oil. So unfortunately, we can't get this effect from over-the-counter fish oils.

MG: No, I agree. Unfortunately, we can't. But now at least we have this option for our patients with residual risk with really outstanding results in the REDUCE-IT trial. Shaun, I really want to thank you. It's always fun chatting with you about these topics. So thanks for joining us today. Thanks as well to HLS Therapeutics for their grant allowing CCRN to develop this podcast. Don't forget to follow this page on your favorite listening platform so you can access new programs as they become available. As a reminder, you can also listen to this program at MD-Online.com. And there you can also access program slides and a transcript of today's program. Shaun, thanks so much.

SG: Thank you.

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